

AMENDMENTS TO THE CLAIMS

The following listing of claims will replace all prior versions and listings of claims in the application.

IN THE CLAIMS:

1. (Currently amended) A ~~double-stranded short interfering~~ chemically modified nucleic acid (~~siNA~~) molecule, wherein: that down-regulates expression of a beta-secretase (BACE) gene; ~~wherein said siNA molecule comprises about 21 nucleotides.~~
 - (a) the nucleic acid molecule comprises a sense strand and a separate antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides;
 - (b) each strand of the nucleic acid molecule is independently 18 to 27 nucleotides in length;
 - (c) an 18 to 27 nucleotide sequence of the antisense strand of the nucleic acid molecule is complementary to a human beta-secretase (BACE) RNA sequence comprising SEQ ID NO:709;
 - (d) an 18 to 27 nucleotide sequence of the sense strand of the nucleic acid molecule is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of the human BACE RNA sequence;
 - (e) 50 to 100 percent of the nucleotides in the sense strand and 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications independently selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications; and
 - (f) one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2'-O-methyl purine nucleotides and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule are 2'-deoxy-2'-fluoro pyrimidine nucleotides.
2. (Canceled)

3. (Currently amended) The ~~siNA~~ nucleic acid molecule of claim 1, wherein said ~~siNA~~ nucleic acid molecule comprises one or more ribonucleotides.
- 4.-36. (Canceled)
37. (New) The nucleic acid molecule of claim 1, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more of the purine nucleotides present in said sense strand are 2'-deoxy purine nucleotides.
38. (New) The nucleic acid molecule of claim 1, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more of the pyrimidine nucleotides present in said sense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides.
39. (New) The nucleic acid molecule of claim 1, wherein the sense strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand.
40. (New) The nucleic acid molecule of claim 39, wherein said terminal cap moiety is an inverted deoxy abasic moiety.
41. (New) The nucleic acid molecule of claim 1, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more of the pyrimidine nucleotides present in said antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides.
42. (New) The nucleic acid molecule of claim 1, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more of the purine nucleotides present in the antisense strand are 2'-O-methyl purine nucleotides.
43. (New) The nucleic acid molecule of claim 1, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more of the purine nucleotides present in said antisense strand are 2'-deoxy purine nucleotides.
44. (New) The nucleic acid molecule of claim 1, wherein said antisense strand includes a terminal phosphorothioate internucleotide linkage at the 3'-end of said antisense strand.
45. (New) The nucleic acid molecule of claim 1, wherein the 5'-end of said antisense strand includes a terminal phosphate group.
46. (New) The nucleic acid molecule of claim 1, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more of the pyrimidine nucleotides present in the sense strand are 2'-O-methyl pyrimidine nucleotides.

47. (New) The nucleic acid molecule of claim 1, wherein 1, 2, or 3 of the purine nucleotides present in the sense strand are 2'-O-methyl purine nucleotides.
48. (New) The nucleic acid molecule of claim 1, wherein the antisense strand, sense strand, or both the antisense strand and sense strand include a 3'-overhang of 1-3 nucleotides.
49. (New) The nucleic acid molecule of claim 48, wherein the nucleotides of the 3'-overhang are chemically modified to comprise one or more phosphorothioate internucleotide linkages, 2'-O-methyl ribonucleotides, 2'-deoxy-2'-fluoro ribonucleotides, 2'-deoxy ribonucleotides, universal base nucleotides, 5-C-methyl nucleotides, inverted deoxybasic moieties or a combination thereof.
50. (New) The nucleic acid molecule of claim 1, wherein said nucleic acid molecule further includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages in the sense strand, the antisense strand, or both the sense strand and the antisense strand.
51. (New) The nucleic acid molecule of claim 1, wherein said nucleic acid molecule further includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more 2'-O-methoxyethyl (MOE) nucleotides in the sense strand, the antisense strand, or both the sense strand and the antisense strand.
52. (New) The nucleic acid molecule of claim 1, wherein said nucleic acid molecule further includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more locked nucleic acid (LNA) nucleotides in the sense strand, the antisense strand, or both the sense strand and the antisense strand.
53. (New) A composition comprising the nucleic acid molecule of claim 1 in a pharmaceutically acceptable carrier or diluent.
54. (New) A chemically modified nucleic acid molecule comprising a sense strand and a separate antisense strand, wherein:
- (a) each strand of said nucleic acid molecule is independently 18 to 27 nucleotides in length;
 - (b) an 18 to 27 nucleotide sequence of the antisense strand of said nucleic acid molecule is complementary to a human BACE RNA sequence comprising SEQ ID NO:709;

- (c) an 18 to 27 nucleotide sequence of the sense strand of said nucleic acid molecule is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of the human BACE RNA sequence;
 - (d) the sense strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends;
 - (e) one or more of the nucleotides present in the sense strand, the antisense strand, or both the sense strand and antisense strand, are 2'-O-methyl modified nucleotides; and
 - (f) one to ten or more of the pyrimidine nucleotides present in the sense strand and one to ten or more of the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides.
55. (New) A composition comprising the nucleic acid molecule of claim 54 in a pharmaceutically acceptable carrier or diluent.
56. (New) A chemically modified nucleic acid molecule, wherein:
- (a) the nucleic acid molecule comprises a sense strand and a separate antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides;
 - (b) each strand of the nucleic acid molecule is independently 18 to 27 nucleotides in length;
 - (c) an 18 to 27 nucleotide sequence of the antisense strand of the nucleic acid molecule is complementary to a human BACE RNA sequence comprising SEQ ID NO:709;
 - (d) an 18 to 27 nucleotide sequence of the sense strand of the nucleic acid molecule is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of the human BACE RNA sequence;
 - (e) at least 35% of the nucleotides of each strand of said nucleic acid molecule comprise modified nucleotides having a modification selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications;
 - (f) at least one of said modifications is a 2'-O-methyl modification; and

(g) at least two of said modifications are different from each other.

57. (New) A composition comprising the nucleic acid molecule of claim 56 in a pharmaceutically acceptable carrier or diluent.
58. (New) A method of modulating the expression of human BACE gene in a cell, comprising administering the chemically modified nucleic acid molecule of claim 1 to the cell under conditions suitable for modulating the expression of BACE gene in the cell.
59. (New) A method of modulating the expression of human BACE gene in a cell, comprising, administering the chemically modified nucleic acid molecule of claim 56 to the cell under conditions suitable for modulating the expression of BACE gene in the cell.